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RESEARCH ARTICLE

NOBLE METAL NANOPARTICLES IN CANCER THERAPY: PROPERTIES CHALLENGES AND CLIN ICAL APPLICATIONS.

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Abstract

Cancer is still one of the most dangerous diseases worldwide. The appli cation of nanotechnology in medicine, known as nano medicine, has pa ved a way for introduction of nanoparticles in treating serious disease s uch as cancer. Nanotechnology differentiates cancer cells from normal cells by active and passive targeting which is essential in cancer treatm ent. Metal nanoparticle find application in cancer diagnosis, treatment a nd monitoring all in a single product enhance patient compliance and m inimising potential adverse effects. Gold and silver are known as noble metals and the nanoparticles fabricated from these noble metals find nu mber of applications in cancer imaging, photodiode therapy, hyperther mia and tissue targeting and they enable clinicians in early diagnosis an d treatment of various cancer. The safety issues mainly toxicity on long time usages of this noble metal nanoparticles are to be addressed. This review highlights the unique properties, clinical applications of noble m etal nanoparticles and its challenges.

Introduction:-

Cancer, a disease categorized by the uncontrolled growth and spread of abnormal cells. The global burdenis expecte d to grow to 21.7 million new cancer cases and 13 million cancer deaths. According to American cancer society, abo ut 1,668,780 new cancer cases are expected are to be diagnosed in 2017. Surgery, radiation, chemotherapy and novel methods such as hormone therapy, photodynamic therapy (PDT) treatments using nanoparticles and eventually com binations of lasers and nanoparticles are the current treatment practices of cancer [(1)]. Indian Council of Medical Rese arch (ICMR) is projected in in 2016 the total number of new cancer cases is expected to be around 14.5 lakh and the figure is likely to reach nearly 17.3 lakh new cases in 2020. Many cancer can be avoided by regular good habits suc h as non-smoking, healthy diet and healthy lifestyle, but Nonetheless, several cancers cannot be avoided by simple b ehavioural changes and require technological innovation to improve outcomes [(2)].

Inspite of many research works in oncology, cancer is still one of the most dangerous diseases in the world.The need for an advanced technology to play an significant role in treating cancer is clearly evident in the statistics indicating that cancer incidence, prevalence, and mortality remain at exceedingly high levels [(3)].The primary aim in treating can cer should focus on increasing the treatment efficacy as well as minimising the side effects. This can be achieved thr ough nanotechnology where it has got potential advantage targeting cancer cells. Nanotechnology is a smart technol ogy which produces systems. Those systems are known as nanoparticles (NPs) comprised many materials such as lip ids virus and metals or devices such as carbon nanotubes and nanowires [(4)].Nanotechnology distinguishes malignant

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cells from non-malignant cells by active and passive targeting which is essential in cancer treatment. Enhanced perm eability and retention (EPR) effect and increasing concentration of nanoparticles (NPs) in the tumor are possible by passive targeting [5].Active targeting [6] will involve selective molecular recognition of antigens, often proteins, that a re expressed on the cancer cells surface so as to localize NPs to malignant cells or, on the other hand, exploits bioche mical properties linked with malignancy such as matrix metalloproteinase secretion. Passive and active targeting ma y be deployed independently, or the two approaches may be combined.

The characteristic properties of nanoparticles include smaller size and larger surface to volume ratio, tunability of ph ysical and chemical properties based on the requirement of size and shape, target binding. Nanoparticles morpholog y is the main cause for their properties [7].In general, nanoparticles used in the field of biotechnology range in particl e size between 10 and 500 nm, seldom exceeding 700 nm. Nanoparticle contain fluorophore, due to this property i t finds more application in diagnosis of cancer. Molecular fluorophores make them ideal for bio diagnostic ap plications.

Metal nanoparticles:-

Nanoparticles are characterized new versatile agents in treating cancer. Metal nanoparticles are obtained from metal precursors. Among several applications, metal nanoparticles (composed of high-Z atoms) were used as selective tum or cell radio sensitizers. [8] Metal nanoparticles thus potential increase radiotherapy efficiency is influenced by metal nanoparticles with the minimisation of its side effects. The word metal nanoparticle describes nanosized metals of si ze 1-100nm.

Metal nanoparticle find application in cancer diagnosis, treatment and monitoring all in a single product enhance pat ient compliance and minimising potential adverse effects. In this review article we discuss about the properties of na noparticles which make then ideal candidates for cancer diagnosis and treatment and their recent applications.

Metal nanoparticles in cancer diagnosis and treatment:-

Since gold and silver exhibit strong absorption and plasmon resonance light scattering, they have wide applications i n cell imaging and DNA hybridization detection, proteins interaction and radiation therapy. Unique optical propertie s, facile surface chemistry, and appropriate size scale of silver and gold nanoparticles draw an appeal of its usage in diagnosis of cancer and its treatment. These silver and gold nanoparticles widely used as anti-tumor agents by diag nosing tumors as well as in therapy by conjugating them with specific ligands and biomarkers. These nanoparticles a re administered topically, by intravascular route or intra operatively.

Due to reduced agglomerating tendency, tendency to mask against immune system and biocompatibility of Poly Eth ylene Glycol (PEG) coating, PEG coated silver or gold nano particles are also employed as carrier in anticancer che motherapeutics. This intravenously administered PEG coated gold or silver nanoparticles retain a longer duration in solid tumors, then this nanoparticles enhanced can be ablated selectively by NIR irradiation. Molecular specific ima ging and treatment of cancer is easily achieved by the synthetic conjugation of the nanoparticles with antibodies targ eted to receptors overexpressed on the cancer cells.

Silver-based nanostructured materials can be used as bio imaging labels for human lung cancer H1299 cells as report ed. [9]

Silver:-

Silver is a soft, white, lustrous transition metal possessing high electrical and thermal conductivity. It has been know n longer than the recorded history due to its medical and therapeutic benefits before the realization that microbes are agents for infections.

Silver nanoparticles (SNPs) are of special interest of remarkable antimicrobial and localized surface plasmon resona nce properties, due to which they have got properties such as broad-spectrum antimicrobial, surface-enhanced Rama n spectroscopy (SERS), chemical /biological sensors and biomedicine materials, biomarker [10] and soon.

The factors which influence the biological activity of SNPs are size, size distribution, surface chemistry, shape, par ticle composition, particle morphology, coating/capping, particle reactivity in solution, agglomeration, and dissoluti on rate, efficiency of ion release, and cell type, and the type of reducing agents used for the synthesis of SNPs are a crucial factor for the determination of cytotoxicity [11].

The scattering, absorption cross section, extinction, and quadrupolar coupling of different silver nanoparticles exami ned reveal that the optical properties depend on the size of the nanoparticles. [12]

Dermal toxicity tests conducted in mice and guinea pigs revealed that short-term exposure to the colloidal SNPs is n ontoxic in oral, ocular but at the same time and long-term toxicity studies are necessary for the safe use of the colloi dal SNP. [13] Silver-based nanostructured materials can be used as bio imaging labels for human lung cancer H1299 cells as already reported. In fact, the surface plasmon resonance and large effective scattering cross-section of indivi dual silver nanoparticles make them ideal candidates for molecular labeling. Thus many targeted silver oxide nanopr obes are currently being developed.

SNPs not only induce apoptosis but also sensitize cancer cells and programmed cell death was concentration-depend ent under conditions.[14] The anticancer property of starch-coated SNPs was studied in normal human lung fibroblast cells (IMR-90) and human glioblastoma cells (U251). SNPs induced changes in cell morphology, decreased cell via bility and metabolic activity, and increased oxidative stress leading to mitochondrial damage and increased producti on of reactive oxygen species (ROS), ending with DNA damage. Among these two cell types, U251 cells showed m ore sensitivity than IMR-90]. Cellular uptake of SNPs occurred mainly through endocytosis.

Multifunctional silver-embedded magnetic nanoparticles consisting of a thick silica shell with silver having an avera ge size of 16 nm; produce strong surface-enhanced Raman scattering (SERS) signals and have magnetic properties, and these two significant properties were used for targeting breast-cancer cells (SKBR3) and floating leukaemia cell s (SP2/O). The antineoplastic activities of protein-conjugated silver sulfide nano-crystals are size dependent in huma n hepatocellular carcinoma Bel-7402 and C6 glioma cells [15]. Chitosan as a carrier molecule for the delivery of silve r to the cancer cells. For example, Chitosan-based nanocarrier (NC) delivery of SNPs induces apoptosis at very low concentrations. Lower concentrations of nanocarrier with SNPs showed better inhibitory results than SNPs alone. C hitosan-coated silver nanotriangles (Chit-AgNTs) show an increased cell mortality rate [16]cytotoxic effect of various sizes of SNPs was significant in acute myeloid leukemia (AML) cells.

Bacterial SNP and fungal extract-produced SNP exhibited anticancer property in human breast cancer MDA-MB-23 1 cells. Both biologically produced SNPs exhibited significant cytotoxicity. Plant extract-mediated synthesis of SNP s showed more significant toxic effect in human lung carcinoma cells (A549) than non-cancer cells like human lung cells, indicating that SNPs could target cell-specific toxicity, which could be the lower level of pH in the cancer cell s

Multifunctional nanocomposites with polymeric nanoparticles (PNPs) containing alisertib (Ali) and SNPs. PNPs con jugated with a chlorotoxin (Ali@PNPs–Cltx) showed a nonlinear dose–effect relationship, whereas the toxicity of A g/Ali@PNPs–Cltx remained stable.[17] Biologically synthesized SNPs exhibited significant toxicity in MCF7 and T4 7D cancer cells by higher endocytic activity than MCF10-A normal breast cell line . Only 40% cell inhibition agains t human breast cancer cells (MDA-MB-231) was observed using silver nanoparticles synthesized from *Acalypha ind ica* [18]. SNP (protein lipid nanoparticles) obtained from seed extract of *Sterculia foetida* (L.) exhibited cellular DNA fragmentation against Hela cancer cell lines [19]. *Datura inoxia*-SNPs inhibited 50% proliferation of human breast ca ncer cell line MCF7 at 20 μg/mL after 24 h incubation by suppressing its growth, arresting the cell cycle phases, and reducing DNA synthesis to induce apoptosis. At a concentration of 25 μg/mL, *Chrysanthemum indicum*-SNPs exhib ited no toxicity against 3T3 mouse embryo fibroblast cells . The differences in their level of anticancer activity again st A375 skin melanoma cells was noticed for the SNPs synthesized using the ethanolic extracts of *Phytolacca decan dra, Gelsemium sempervirens, Hydrastis canadensis,* and *Thuja occidentalis.*

SNPs synthesized from *Ficus religiosa* was effective at a dose 50 μg/mL against the DAL induced mice model (30– 35 g). Silver nanoparticles produced using *Origanum vulgare* exhibited dose dependent response for t human lung c ancer A549 cell line (LD50–100 μg/mL) [20].The complete apoptosis (95%) was observed at 25 μL/mL of *Alternanth era sessilis*-assisted SNPs for prostate cancer cell (PC3), whereas 99% growth inhibition was obtained for breast can cer cells (MCF-7) [21] .Like these many silver nanoparticle against cancer from herbal source were reported [22].

It is reported that SPs are capable to kill osteosarcoma cells independently from their actual p53 status and induc e p53-independent cancer cell apoptosis. This feature renders SNPs attractive candidates for novel chemotherap eutic approaches. And then found that SNPs significantly suppressed the H1299 tumor growth in a xenograft severe combined immune deficient (SCID) mouse model. The results revealed that the anticancer activities of SNPs, sugge

sting that they may act as potential beneficial molecules in lung cancer chemoprevention and chemotherapy, especia lly for early-stage intervention. Reports on in vivo antitumor activity of SNPs are also very limited. It is demonstrat ed the efficacy of biologically synthesized SNPs as potential anticancer molecules that were shown to have a potent inhibitory activity on disease progression and a potent restorative effect in a Dalton's lymphoma ascites tumor-beari ng mouse model. Intramuscular administration of silver and SNPs significantly increased mice survival at day 35 (7 0% and 60% survival, respectively) in L5178Y-R tumor-bearing mouse model. [23] This finding indicated that SNPs showed anticancer activity in vivo. Though SNPs as an antitumor agent can provide new opportunity for medical sci ence, more studies are still needed to advance to clinical translation. When molecular mechanisms, signal pathways, and especially in vivo anticancer efficiency, are better understood, the applications of SNPs can be expected to expa nd further.The SNPs possess several features such as simple synthesis route, high surface to volume ration, adeq uate and tunable morphology, intracellular delivery system, characteristic, a large plasmon field area.

Preparation of SNPs:-

SNPS have been prepared by two methods known as physical and chemical methods evaporation-condensation usin g a tube furnace, spark discharging and pyrolysis are physical methods. Merits of physical method are speed, radiati on used as reducing agents , and no hazardous chemicals involved , but it produce low yield and high energy consu mption, solvent contamination, and lack of uniform distribution at atmospheric pressure

Chemical methods include usage of water or organic solvents to synthesize the silver nanoparticles. This process usu ally employs three main components, such as metal precursors, reducing agents, and stabilizing/capping agents. Rec ently researches synthesise SNP by green chemistry approach which avoids all demerits of chemical methods. [24]

Charecterization of SNPs:-

Characterization of SNPs have been performed by a variety of analytical methods such as UV-vis spectroscopy, F ourier transform infrared spectroscopy (FTIR), X-ray diffractometry (XRD), X-ray photoelectron spectroscopy (XP S), Scanning electron microscopy (SEM), transmission electron microscopy (TEM), dynamic light scattering (DLS), sand atomic force microscopy (AFM).[25]

Challenges in cancer treatment using SNPs:-

Inspite of several nanoparticles developed various methods; the main challenge is the heterogeneity of the tumor and its stroma in targeting cancer cells. Even though nanoparticles is the single platform which address the issues relate d achieving higher specificity, minimising toxicity, biocompatibility, safety, better efficacy, overcoming the pitfalls of the conventional chemotherapy, the field of nanoparticles in cancer treatment need to address several challenge ; these include variability of nanoparticles, physiological barriers, enhanced permeability and retention effect, limite d carrying capacity, and regulatory and manufacturing issues. [26]

Gold:-

Gold nanoparticles (GNP) contain colloidal gold which differs in properties that of bulk gold. Due to optical properti es with light as suggested by Michael Faraday, these particles are in red color for size less than 100nm or yellowish color for larger sizes. Metal nanoparticles contain free electrons oscillate with respect to the metal lattice in oscillati ng electromagnetic field of the light [27]. This process is resonant at a particular frequency of the light and is the local ized surface plasmon resonance (LSPR). After absorption, the surface plasmon decays radiatively causes light scatte ring or nonradiatively by converting the absorbed light into heat. Due to this reason gold nanospheres of 10 nm in di ameter have a strong absorption maximum around 520 nm in aqueous solution due to their LSPR.

The shape of the colloidal nanoparticle has got significant role in its properties. Due to their two resonances such as plasmon oscillation along the nanorod short axis and plasmon oscillation along the long axis the color of the particle solution is more vivid for rods than spheres. Since rod shaped particles have absorption peak on transversely as well as longitudinally their anisotropy affects its assembly, they are much used in biological imaging, electronics etc. The less hazardous nature due to their chemical stability, simple and direct synthesis, biocompatibility, non interfering w ith biomarkers are major reasons for the extensive use of GNP for the diagnosis of cancer[28].In animal experiments, GNPs were preferentially sequestered by tumors and, upon irradiation, locally enhanced the dose by emitting shower s of Auger electrons .

Among different nanostructures gold nanoparticles are the most appropriate candidate in photothermal sensitizing fo r the following reasons: they powerfully absorb laser light, are nontoxic, easily conjugates with proteins and antibodi es and have tuneable optical properties [29].

GNP Prepararion:-

Gold nanoparticle of specific application has been developed for spherical and non-spherical shapes [30] syntheised s pherical GNP and later that refined the processing (1973). By this method hydrogen tetrachloroaurate ($HAuCl_4$) gold salts have been reduced chemically .citrate serves as a reducing agent in this reduction process and produced GNP o f 10-20 nm in diameter. Breown and Natan synthesised GNP of *via* seeding of Au^{3+} by hydroxylamine.[31] Subseque nt research led to the modification of the shape of these gold nanoparticles resulting in rod, triangular, polygonal rod s, and spherical particles.[32] These gold nanoparticles have proved a high surface area to volume ratio with unique pr operties. They have conjucation capacity with ligands. Due to this the GNP has wider application in imaging and dia gnosis of various disease states.

EI syaed used GNP in cancer imaging by selectively transporting GNPs into cancer cell nucleus by conjugating argi nine–glycine–aspartic acid peptide (RGD) to enable cancer-cell-specific targeting and a nuclear localization signal peptide (NLS) will exhibit cancer cell nucleus specific targeting to a 30-nm GNPs *via* PEG[33].Gold-based spherical nanoparticle nucleic acid [Bcl2L12 siRNA] delivery crossed BBB and accumulated in human glioma tumors in mic e to silence target gene and reduce tumor burden . Gold and silica nanoparticles containing endothelial growth factor [VEGF]-targeted nanoshell's for thermal ablation and vessel disruption in mouse glioma model and it is in clinical tr ials for head and neck cancer and primary and/or metastatic lung tumors. [34]

Current research field present a variety of nanoparticles, and each has its own unique properties and applications suc h as nanorings, nanoshells, nanorods, nanopores and nanowires, etc.

Nanoprobes:-

Tumor-targeted gold nanoparticles was developed as a probe for Raman scatters *in vivo*. These GNP were coded wit h Raman reporter and further encapsulated with a thiol-modified PEG coat. The results obtained by Qian and cowor kers suggest the highly specific recognition and detection of human cancer cells, as well as active targeting of EGFR -positive tumor xenografts in animal models can be made using SERS.

Nanorods:-

Moreover, the use of gold nanorods as photothermal agents sets them apart from all nanoprobes. The heat is the actu al method of therapy that kills the targeted cells. One of the biggest recent successes in photothermal therapy is the u se of gold nanoparticles. The peak absorptions of spherical GNM have been limited to 520 nm for 10 nm diameter a nd Moreover, skin, tissues, and haemoglobin have a transmission window from 650 up to 900 nm.

Gold nanorods by Murphy and Coworkers, who were able to tune the absorption peak of these nanoparticles, which can also be tuned from 550 nm up to 1 μm just by altering its aspect ratio of the nanorods. Hence, for the rod-shaped gold nanoparticles with the absorption in the IR region, when selectively accumulated in tumors when bathed in las er light (in the IR region), the surrounding tissue is barely warmed, but the nanorods convert light to heat, killing the malignant cells [35].

Nanoshells:-

Nanoshells are optically tuneable core/shell nanoparticles that can be prepared to strongly absorb in the near-infrared (NIR) region where light transmits deeply into tissue. As these particles the enhanced permeability and retention (E PR) effect, they accumulate in the tumor and induce photo thermal ablation of the tumor when irradiated with an NI R laser. Tumor specificity is enhanced via functionalizing the nanoshell surface with tumor-targeting moieties. Nano shells can also be fabricated to strongly scatter light and therefore can be used in various imaging techniques such as s such as optical coherence tomography (OCT) and dark-field microscopy.

It is reported the usage of near-infrared resonant nanoshells for whole-blood immunoassays. Multifunctional magnet ic gold nanoshells (Mag-GNS) was developed with utilizing Fe_3O_4 nanoparticles as the magnetic core. The Fe_3O_4 na noparticles allow MRI for diagnosis, and the gold nanoshells enable photothermal therapy. By attaching an antibody to the Mag-GNS by a PEG linker, cancer cells can be targeted. Once localized, these particles enable the detection o f cancer using MRI, whereas the photothermal therapy can be used to get rid of cancer cells [36].

Nano cages:-
Nanocages are hollow GNP absorbs in the near infrared range Xia and Co-workers first developed that by reacting s ilver nanoparticles with chloroauric acid ($HAuCI_4$) in boiling water.[37] Their LSPR peaks can also be tuned to the ne ar infrared region by controlling the thickness and porosity of the walls., they have found applications in drug delive ry and/or controlled drug release as that of nanoshells and the hollow interiors can host small objects such as magne tic nanoparticles to construct multifunctional hybrid nanostructures diagnostic imaging and therapy.

Nanoclusters:-
In current years, photoluminescent gold nanoclusters have gained considerable interest in both fundamental biomedi cal research and practical applications. Salient features of nanoclusters such as their unique molecule-like optical pro perties, ultra small size, and facile synthesis gold nanoclusters have been considered very promising photoluminesce nt agents for bio sensing, bio imaging, and targeted therapy. The cellular uptake and cytotoxicity of Au NCs along w ith intracellular generation of reactive oxygen species in MCF-7 and MDA-MB-231 breast cancer cells D Gold etha nesulfonic acid nanocluster showed exposure time-dependent high cytotoxicity and higher reactivity in breast cance r cells ,which led increased generation of reactive oxygen species[38].

Nanostars:-
In recent year a new type of nanoparticle developed which is known as “nanostars," which accumulate in tumor cells and scatter light, thus tumors become easily seen with the help of a special camera. The particles are in the size abo ut are each about 140 nm across, and consist of eight-point gold stars that are surrounded by a layer of dye and encas ed in a sphere of silica and a polymer.

Gold Nanostars characterised as a star-shaped gold core, a Raman reporter resonant in the near-infrared spectrum, an d a primer-free silication method. In genetically engineered mouse models of breast cancer, pancreatic cancer, prosta te cancer, and sarcoma, and in one human sarcoma xenograft model, nanostars enabled accurate detection of macros copic malignant lesions, as well as microscopic disease, without the need for a targeting moiety. The sensitivity (1.5 fM limit of detection) of surface-enhanced resonance Raman scattering nanostars permitted imaging of premalignan t lesions of pancreatic and prostatic neoplasias. High sensitivity and broad applicability, in conjunction with their ine rt gold-silica composition, render SERRS nanostars a promising imaging agent for more precise cancer imaging and resection. [39]

The plasmonic heating response of nanostar serves as a signature of nanoparticle internalization in cells, bringing the ultimate goal of nanoparticle-mediated photothermal therapy a step closer. Gold nanostars can be used for simultan eous photoacoustic imaging and photothermal therapy in living cancer cell. [40]

Characterization of GNPs:-
UV–Vis Spectrophotometry:-
The optical properties of the gold colloidal solution were monitored in UV spectrophotometer in the range of 300–7 00 nm.

Transmission Electron Microscopy:-
Samples for TEM analysis were prepared by placing a drop of the gold colloidal solutions on carbon-coated copper TEM grids. The sample deposited on the grid was allowed to dry in air for a few minutes before analysis. The morph ology and the size of the prepared gold nanoparticles were determined by transmission electron microscope.

Dynamic Light Scattering (DLS):-
Determination of particles’ size distribution was carried out with Zetasizer by illuminating the gold colloidal solutio n with He–Ne Laser.

Toxicity:-
Nanoparticles will accumulate in various cells. But the size of the nanoparticle plays a significant role in avoidance i n renal clearance and immune activation, resulting in enhanced circulation time of nanoparticles and availability for their effective treatment. [41]

Challenges:-

Challenges in gold nanoparticle include, factors influencing pharmacological properties are to be clarified, long term cytotoxic effects must be studied, inflammatory and immune response triggered by some polymer coating must be el iminated, cost of the therapy must be minimised.

Challenges for noble metal nanoparticles:-

A major drawback in translating gold and silver and other inorganic nanoparticles to clinical practice in targeting ca ncer cells is their non-biodegradable nature. And the next issue governs the size of the nanoparticle for body clearan ce .They is too large for body clearance in desirable time frames. This leads to issues related to accumulation and ch ronic toxicity of nanoparticle. Recent research reveal that nanoparticles of size less than 5, 5, nm are effectively elim inated by urinary excretion. But, plasmonic nanoparticles with resonances in the NIR region are at least 50 nm in siz e, and often > 100 nm, severely limiting their body clearance rates.[(42)]

Conclusion and future prospective:-

Nanoparticles have gained immense interest as next generation thernostic tool in cancer. These nanoparticles overco me several demerits of conventional chemotherapy, such as adverse effects and the development of resistance. They help clinicians not only in early diagnosis but also in monitoring the progress and success of therapy. Many studies h ave proved their potential in cancer therapy, and various formulations of noble metal nanoparticles are already in the preclinical and clinical stages of development. Despite the many proposed advantages of noble nanoparticles the ag gregate or disintegrated nanoparticles can be toxic and attempt is required to make their desirable properties intact u nder physiological conditions. There are many potentially toxic effects linked with exposure to inorganic nanoparticl es, such as the generation of reactive oxygen species, formation of apoptotic bodies, and impaired mitochondrial fun ction. The evaluation of the safety of rigid nanoparticle, especially for long-term application, is a major challenge. T he chronic toxicity and mechanisms related to metabolism of rigid nanoparticles in the body are to be discussed befo re potential clinical applications. Thus, it is vital to find standard guidelines/protocols for the toxicity determination of rigid nanoparticles *in vitro* and *in vivo*. The safety issues are currently taken onto consideration and should gain more focus future studies. However, there is no doubt that, once these issues are successfully addressed, noble metal nanoparticles will become an important clinical tool in cancer therapy.

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